

Original article

Pathologic features of colorectal carcinomas associated with Crohn's disease in Korean population



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ABSTRACT

Background: Colorectal cancer (CRC) has been known to complicate Crohn's disease (CD). Several reports in Western population revealed that CRC in CD were characterized by much younger onset and equal distribution of tumors along the entire colon. However, clinicopathologic features of CD-associated CRC in Korean population have not been well documented yet.

Methods: Among 2968 Korean CD patients, 16 patients (0.54%) were found to develop CRC during follow up. We reviewed clinicopathologic features of the 16 CRC patients.

Results: The mean age at the time of CRC diagnosis was 39.3 years (range 18–59 years) and 14 of the 16 CRCs (87.5%) occurred in anorectal region. Mucinous adenocarcinoma was strikingly frequent (9/16, 56.3%) and eight cases (8/9) of the mucinous adenocarcinoma cases were located at anorectal area. The other cases consisted of 4 tubular adenocarcinomas, 2 signet ring cell carcinomas and 1 neuroendocrine tumor. Thirteen patients (81.3%) had a history of perianal fistula and 8 of them had a histological association between the CRC and the perianal fistula.

Conclusions: CD-associated CRC was characterized by young age at diagnosis, mucinous histology and association with perianal fistula in Korean patients.

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1. Introduction

Crohn's disease (CD) is one of most common types of inflammatory bowel disease (IBD). It could affect the entire gastrointestinal tract but usually involves small and/or large intestine and leads to various complications including bowel stricture, fistula formation, or abscess. Although the prevalence of CD is higher in Western countries than in Asian countries, recent studies have reported that the incidence of CD in Asia is gradually increasing [1–3].

The clinicopathologic characteristics of CD in Asian countries resemble those in Western countries. However, some genetic and clinical features of CD patients in Asian countries differ from those in Western countries. Genetically, tumor necrosis factor superfamily member 15 (*TNFSF15*) mutation was found to be associated

with Korean CD patients whereas nucleotide-binding oligomerization domain protein 2 caspase recruitment domain protein 15 (*NOD2/CARD15*) mutation was found to be frequently associated white and Jewish CD patients [4–8]. Moreover, IL-23 receptor (*IL23R*), autophagy-related 16-like 1 (*ATG16L1*), *IBD5* locus, and the gene desert on chromosome 5p13.1, which are firmly related to CD susceptibility in Caucasians [9,10], showed no association with Korean CD patients [11]. Male predominance, higher prevalence of perianal fistula, and common involvement of both small and large intestine are distinguishing features of CD in Korean population compare to Western population [1,2,12].

Colorectal carcinoma (CRC) has been known to complicate Crohn's disease. Several reports in Western population revealed that CRC in CD were characterized by much younger onset than sporadic CRC and equal distribution of tumors along the entire colon [13,14]. Given the differences in genetic and clinical features between CD patients in Asian and those in Caucasians, it can be expected that the features of CRC associated CD in Asians might be distinguished from those in Caucasians. Although Yano

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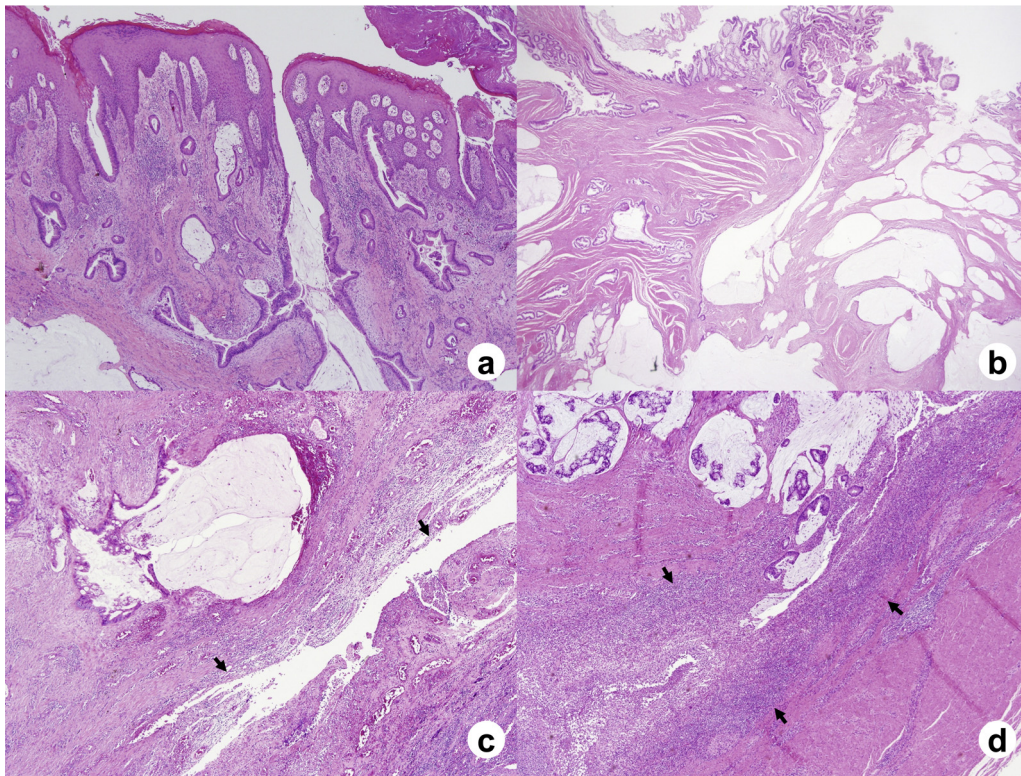


Fig. 1. Histologic features of fistula-associated carcinoma. (a) Extremely well-differentiated tumor glands are observed in deep subepithelial connective tissue in the anus. The adjacent stroma is inflamed and neoplastic glands are radially arranged around the central large tubule suggesting association with anal fistula. (case 11) (b) Well differentiated mucinous carcinoma is deeply seated with disproportionately small mucosal lesion that is characteristic of fistula-associated carcinoma. (case 1) (c) Tumor glands lining a large extracellular mucin pool are very close to the apparent fistulous tract (arrows). (case 5) (d) mucinous tumor glands are found within inflamed fistulous tract (arrows) (case 7) (original magnification for a and d, $\times 40$ objective lens; b and c, $\times 12.5$ objective lens).

et al. reported epidemiology of CRC in Japanese CD patients [15,16], they did not provide detailed comparison of CRC associated CD between Asian and Caucasian populations. Thus, clinicopathologic features of CRC associated with CD in Asian population are not well documented. Regarding to this question, we recently found that CD-associated CRC cases in Korean population frequently occurred in anorectal region in relation to perianal fistula [17]. Here we describe the detailed clinicopathologic features of CRC cases that developed during follow up period of CD patients in Korean population.

2. Materials and methods

2.1. Patients and samples

We retrieved 16 patients who developed CRC during regular follow up among 2968 patients who had been diagnosed with CD prior to diagnosis of CRC between June 1981 and December 2015. Diagnosis of CD was based on conventional criteria involving clinical, radiologic, endoscopic and pathologic findings [2,12]. Any patient with hereditary cancer syndrome or with CRC at the time of diagnosis of CD has been excluded. For each patient, gender, age at diagnosis of CRC, age of CD onset, smoking status, history and status of perianal fistula, age of fistula onset, colonoscopic and radiologic findings, surgical procedure, tumor type, differentiation, location, TNM stage, results of immunohistochemical and molecular studies and outcome were evaluated. Formalin-fixed paraffin-embedded tissues samples were obtained from surgically resected specimen from 14 patients (6 abdominoperineal resection, 2 total proctocolectomy, 4 transanal excision, 1 right hemicolectomy, and 1 left hemicolectomy) and 2 patients had only colonoscopic biopsy mate-

rial. Study protocol was approved by the Institutional Review Board (Protocol number: 2015-1060).

2.2. Pathologic examination

Formalin-fixed, paraffin-embedded samples from tumor and adjacent non-neoplastic tissue were used for Hematoxylin and eosin (H&E), immunohistochemistry (IHC), microsatellite instability (MSI) testing. Gross and microscopic findings were reviewed by two pathologists. When CRC was found in anorectal region, we checked whether the patient had a long-standing history of perianal fistula and reviewed microscopic features with an emphasis on the anatomic relationship between tumor and perianal fistula if surgically resected specimen was available. Fistula-associated carcinoma was diagnosed according to the following criteria: (1) presence of long-standing perianal fistula, (2) deeply seated tumor without major mucosal lesion (Fig. 1A and B), and (3) anatomic association between fistulous tract and tumor cells (Fig. 1C and D). Tumors were staged pathologically according to AJCC TNM stage system, seventh edition. To confirm diagnosis or to screen MSI-positive tumor, IHC staining was performed for synaptophysin (cell marque, CA, USA, 1:200), MLH1 (Novocastra, Newcastle, UK, 1:50) and MSH2 (Pharmingen, New Jersey, USA, 1:400), MSH6 (Cell Marque, California, USA, 1:400) and PMS2 (Cell Marque, California, USA, 1:50) using an automated staining system (BenchMark XT; Ventana Medical Systems, AZ, USA). The MSI status was determined using the five-marker Bethesda panel (BAT25, BAT26, D5S346, D2S123, and D17S250) [18]. Polymerase chain reaction (PCR) products were analyzed using ABI3130 Genetic analyzer version 3.1.1 software (Life technologies, Carlsbad, CA, USA). Tumors were considered

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